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Original article

Pharmacoeconomic evaluation of the MF59 – adjuvanted influenza vaccine in the elderly population in Italy

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Key words

Budget impact analysis • Influenza vaccination • Adjuvanted vaccine

Summary

Introduction. *Influenza vaccination has proven effective in the reduction of influenza-like illness (ILI) cases and influenza-related hospitalizations, drug consumption, primary care consultations and deaths in the elderly population. The aim of this study is the assessment of the financial budget impact of a seasonal vaccination program based on the use of the MF59 adjuvanted vaccine as compared with the traditional vaccine or the absence of vaccination in Italian elderly population.*
Methods. *A pharmacoeconomic simulation model was developed to simulate the effect of the three different vaccination programs during a single influenza season. Health economics and demographic data were taken from specific Italian sources, and vaccine effectiveness data derived from published literature. Direct medical costs were considered according to current Italian prices and tariffs.*
Results. *About 83% of the 12 million people of at least 65 years of age currently resident in Italy can be considered at high risk for influenza complications due to underlying chronic diseases. Absence of vaccination could lead to more than 2 million ILI cases, and 29,000 related deaths. The vaccination program with a coverage rate of 65.6% would lead to an estimated 1.5 million ILI cases (26.9% reduction) with a standard vaccine and to 1.3 million (35.8% reduction) with the MF59 adjuvanted vaccine with a relative increase of avoided cases of 33,1%. The standard vaccination program produced a moderate direct cost increase of about 50 million Euro (+4.6%), whereas the adjuvanted vaccine provided an estimated saving of about 74 million Euro (-6.8%), both compared to the non vaccination. Cost savings were mainly related to hospital admissions avoided in the elderly population (≥ 65 years of age).*
Conclusions. *The vaccination with the MF59 adjuvanted vaccine resulted more effective and cost saving when compared with the standard vaccination and with no vaccination, thus representing the optimal strategy for the elderly population. The standard vaccine, even though a light cost increase, still proved to be effective compared to the null option, with the initial cost for the vaccination program nearly offset by healthcare resources savings obtained during the season.*

Introduction

The influenza infection is characterized by a high mutation rate of the virus responsible for it which has the capability to evade the host immune response, causing the repetition of seasonal epidemics. Because of its high social impact, influenza seasonal epidemic represents a huge healthcare issue worldwide, being one of the major causes of seasonal morbidity, hospitalizations and mortality, particularly in the elderly population. Aging subjects face a higher risk of complications because of the natural decline of their immune response and for this reason this population represents one of the main target for the annual influenza vaccination program in Italy.
The MF59 adjuvanted vaccine (Fluad®) is authorized in European countries since 1997, for the seasonal influenza vaccination. MF59 adjuvant is an oil/water emulsion containing squalene, a metabolic intermediate of cholesterol synthesis, which is contained in the plasma membrane. Results of several clinical trials demonstrate a significant immunological superiority of this vaccine with respect to the traditional vaccine in the elderly population, because it induces a greater antibody response, particularly in the high-risk patients (people affected by chronic o degenerative diseases, such vascular, metabolic o respiratory diseases) [1, 2]. The MF59 adjuvanted vaccine confers also a higher protection versus heterovariant influenza virus strains, which correspond only partially to the strains included in the seasonal vaccine [3].
In recent years budget impact analyses has become an essential part of the economic evaluation of health care interventions. The purpose of such a pharmacoeconomic analysis is to evaluate the financial impact on health care expenditure (and thus the affordability for the payer) of the adoption of a new intervention with respect to other viable alternatives. The use of analytic models to perform the simulation of outcomes and associated costs, to better inform a comprehensive choice, is well established [4].
The aim of this study is the assessment of the financial budget impact of a seasonal vaccination program based on the use of the MF59 adjuvanted vaccine as compared with the traditional vaccine or the absence of vaccination in Italian elderly population.

Methods

A pharmacoeconomic simulation model has been developed in Microsoft Excel to simulate the effect of three different vaccination programs in the Italian elderly population, during a single influenza season. Three alternative programs have been evaluated: 1) the vaccination with a standard vaccine (split or sub-unit); 2) the vaccination with the MF59 vaccine; 3) no intervention. The principal effects of the vaccination considered in the model were related to the incidence of influenza-like illness (ILI) cases, influenza-related complications, and mortality. In detail the following events were simulated on the time horizon of influenza season: ILI cases; hospitalizations for influenza or pneumonia; hospitalizations for other respiratory diseases; hospitalizations for congestive heart failure (CHF), acute coronary syndrome (ACS) or cerebrovascular accident (CVA); death for all causes, during the influenza season.
The administration of the vaccine during the autumnal season to a proportion of the elderly subjects (corresponding to the coverage rate) has been simulated. Effectiveness data for both vaccines were derived from published literature, and referred to a first immunization. This implies that the potential protective effect related to the repetition of the vaccination in subsequent seasons was conservatively neglected.
An alternative scenario was also developed to account for the consequences of a flu epidemic caused by a heterovariant virus strain.

Population of the simulation

The simulation was run over the elderly resident Italian population (data as of 1st January 2010), corresponding to 12,206,470 subjects aged 65+ years [5]. The fraction of this population that could be considered at high risk for influenza-related complication due to the presence of other chronic condition was set to 82.6%, based on the data from a population study on health conditions, risk factors and use of the health services in Italy [6]. A 65.6% coverage rate for the influenza vaccination in the Italian elderly population was considered, based on the data published by the Italian Ministry of Health for the season 2009-2010 [7].

Influenza in the non vaccinated population

The incidence of ILI cases among the non vaccinated population in Italy is largely unknown. Nonetheless some local data are available from the literature (Tab. I) [8, 10]. On the basis of these data a metanalysis was developed with a statistic Bayesian Random Effect model and the use of the WinBUGS software tool. In general, with this statistic model it is assumed that the outcomes recorded for the same phenomenon in different settings could be all ascribed to a common component (characteristic of the phenomenon in itself) added to random variations (specific of the settings). From the metanalysis the incidence of ILI in one season in non vaccinated population resulted 16.8% (CI95%: 6.58-33.1%). Other pharmacoeconomic studies obtained similar estimates: a study from Scuffham and colleagues [11] used an incidence rate of 10% for the UK, France and Germany, a study from Piercy [12] used 5% for France, and another study from Baio used 16.58% for Italy [13].
Incidence rates for influenza related complications (Tab. II) derived from the data published by an early economic model of the economic impact of influenza vaccination in 25 European countries [14]. Regarding the ACS and CVA hospitalizations no data was found for Italy and thus we obtained the values from a Spanish case-control study, conducted in the Valencia province during the influenza season 2004-2005 [15], adapted in the hypothesis of a constant rate of events throughout the entire season.

Effectiveness of influenza vaccines

The effectiveness data for the standard vaccine derived from a comprehensive Cochrane review and metanalysis [16], which examined published effectiveness studies in the prevention of influenza, ILI cases, hospitalizations, complications and mortality in people over 65 years. 4,400 randomized, quasi-randomized, cohort and case-control studies published until the beginning of 2006 were retrieved. 71 studies matched the inclusion criteria and were included in the published metanalysis. In the current budget impact analysis the effectiveness data for mortality and hospitalizations reductions were extracted from the metanalysis of cohort studies and expressed in terms of relative risk (RR) (Tab. II). For the reduction of ILI cases the effectiveness data derived from the metanalysis of Randomized Controlled Trials (RCT) were preferred. This choice was determined by the low quality and lack of homogeneity of the cohort studies analyzed, as evidenced in the published metanalysis. Another consideration that, for ILI reduction, drove the choice for the metanalysis of RCTs instead of cohort studies was the intrinsic bias in them caused by the same definition of ILI which is solely based on clinical, unspecific and not univocal symptoms.
For the MF59 adjuvanted vaccine no field study investigating the vaccine effectiveness in terms of reduction of ILI cases has been found. This lack of evidence is probably linked to the current regulatory asset in which the proof of immunogenicity for an influenza vaccine is considered a sufficient condition for market approval in the US and Europe. In absence of other information, effectiveness data for the adjuvanted vaccine was derived from the immunogenicity evidence, based on the relationship existing between protection rate and immunological power. The MF59 adjuvanted vaccine demonstrated in elderly people a superior immunogenicity with respect to the standard vaccine in all the three viral strains currently circulating (AH3N2, AH1N1 and

B) [1, 2]. These immunogenicity data were converted in effectiveness rates, expressed as RR of ILI cases avoided [12, 17]. In the current budget impact analysis, the mean effectiveness value for the base case (relative to the B strain) was considered, whereas the others were considered for the sensitivity analysis.
The effectiveness data of the MF59 vaccine in reducing hospitalizations for influenza and pneumonia were obtained from a recent Italian population-based cohort study designed to compare the risk of hospitalization for influenza or pneumonia during the influenza season among elderly persons vaccinated with MF59 adjuvanted versus conventional sub-unit influenza vaccine. The study was conducted in three consecutive influenza seasons (2006-2009) through General Practitioners or Local Health Authorities District offices and overall 170,816 person-seasons were recruited and analyzed. Results of the study showed an adjusted risk ratio for influenza and pneumonia hospitalization of 0.77 (95%CI 0.59-0.99) for the MF59 vaccine relative to the traditional one [18]. In the current analysis the RR of the MF59 vs. no vaccination was calculated by multiplication of the RR of the standard vaccine vs. no vaccination by 0.77 (Tab. II).
The reduction of hospitalizations for ACS and CVA (Tab. II) derived from the already mentioned Spanish cohort study [15]. Finally, the effectiveness of the adjuvanted vaccine in reducing mortality derived from the Pellegrini et al. metanalysis [19].
As long as it concerned hospitalizations for respiratory complications and for CHF, no data were found for the adjuvanted vaccine. We thus assumed that the two vaccines could have had the same outcomes per case of ILI. In this way the RR values for the adjuvanted vaccine were calculated by assuming the same number of CHF and respiratory complication events per ILI case as for the standard vaccine, respectively in high and low risk groups. As no data were found for the reduction of ACS and CVA hospitalizations for the standard vaccine, the same concept (with inverted roles) has been adopted to calculate their RR values.

Costs

In the budget impact analysis the perspective of the Italian National Healthcare System (SSN – Servizio Sanitario Nazionale) was adopted, therefore only direct medical costs were considered. In particular the analysis was performed accounting for the cost of acquisition and administration of the vaccines, the cost of the visits and of the pharmaceutical treatments for influenza and the cost for related hospitalizations (Tab. III).
Vaccine cost was valorized by the mean value of the bid prices in public tenders in years 2006-2009. The mean acquisition cost resulted in € 3.81 for a split or subunit vaccine, and in € 5.58 for the adjuvanted vaccine. According to a national survey the influenza vaccine is administered in the GP's room in 69.5% of the cases and in specific vaccine centers or other structures in the remaining part [20]. In the first case the administration cost was considered equivalent to the cost of one GP outpatient visit [21] plus the incentive granted by the Italian SSN to the GP to improve the diffusion of the influenza vaccination among the elderly people [22]. In case of vaccine administration in specific vaccine centers the cost was estimated by considering the monetary value of 5 minutes of work for a hospital attendant and for a medical specialist [23]. On the average the cost for vaccine administration resulted in € 16.23.

Tab. I. Italian population studies considered for the metanalysis of the infection rate.

ILI cases (n)	Exposed subjects (n)	Infection rate (%)	Influenza season	Geographic area	Source
179	2,039	8.8%	2001-2002	Benevento city	[8]
69	222	31.1%	1999-2000	Siena city	[9]
37	206	18.0%	2000-2001	Siena city	[9]
29	208	13.9%	2000-2001	Liguria region	[10]
11	79	13.9%	2000-2001	Milano	[10]

ILI: influenza-like illness.

Tab. II. Outcome rates in the non vaccinated population and risk reductions (expressed as relative risk, RR) with the standard and adjuvanted MF59 vaccine in the elderly population at high/low risk for influenza-related complications.

Events	No vaccine	Standard vaccine		MF59 vaccine	
	Rates for 100 subjects	RR (Low Risk)	RR (High Risk)	RR (Low Risk)	RR (High Risk)
ILI	16.8	0.59	0.59	0.47	0.45
I&P hospitalization	0.32	0.50	0.74	0.39	0.57
Resp. hospitalization	1.08	0.84	0.85	0.68	0.65
CHF hospitalization	0.23	0.79	0.92	0.64	0.70
ACS hospitalization	0.33	0.89	0.94	0.72	0.72
CVA hospitalization	0.51	0.87	0.91	0.70	0.70
Mortality	0.24	0.65	0.39	0.46	0.27

ILI: influenza-like illness; ACS: acute coronary syndrome; CHF: congestive heart failure; CVA: cerebrovascular accident; I&P: influenza and pneumonia; RESP: respiratory complications.

Tab. III. Mean unitary costs considered in the study.

Outcome	Mean cost (Euro)
Standard vaccine acquisition	3.81
Adjuvanted vaccine acquisition	5.58
Vaccine administration	16.23
Visit cost per ILI case	12.83
Pharmaceutical therapy per ILI case	3.21
Hospitalization for I&P (DRG 68, 69, 79, 80, 89, 90, 421)	3,916.63
Hospitalization for Resp. (DRG 68, 69, 79, 80, 87, 89, 90, 92, 93, 94, 95, 96, 97, 101, 102)	3,448.10
Hospitalization for CHF (DRG 127)	3,091.51
Hospitalization for ACS (DRG 121, 122, 123, 140, 144, 145)	3,489.00
Hospitalization for CVA (DRG 14, 15)	3,453.86

ILI: influenza-like illness; ACS: acute coronary syndrome; CHF: congestive heart failure; CVA: cerebrovascular accident; I&P: influenza and pneumonia; RESP: respiratory complications; DRG: Diagnosis Related Group

A large population study [24] showed that in Italy about 60% of the patients ask for a GP consultation in case of influenza [24] and that in about 66% of the cases these are domiciliary visits. Weighing the average costs of GP outpatient and domiciliary visits [21] with these findings resulted in an average visit cost per ILI case of € 12.83. Pharmaceutical treatment of influenza in general consists of antiviral drugs, drugs used for the symptomatic therapy of the illness and antibiotics. Among these only antibiotic costs were considered in the budget impact analysis as the routine use of antiviral drugs is not recommended and symptomatic drugs (acetaminophen, non-steroidal anti-inflammatory drugs, cough drugs) are not currently reimbursed by the Italian SSN. The evaluation of the costs for one antibiotic course was based on the resource consumptions recorded in two Italian cost-benefit studies [9, 10] valorized at current market prices [26].

Hospitalization costs for the Italian SSN were calculated considering national Diagnosis Related Group (DRG) tariffs [27]. As each hospitalization corresponded to more than one DRG code, the tariffs were weighted with the relative occurrence frequencies in the Italian general population over 65 years as recorded in the Italian discharge record database [28] (data 2005).

Mismatch scenario and sensitivity analysis

Influenza vaccines provide protection not only for influenza strains included in their formulations, but also for heterovariant virus strains, with a partially different set of antigens. This effect varies depending on the antigenic difference between the two strains. The MF59 adjuvanted vaccine demonstrated in the elderly population to provide a higher protection against heterovariant virus strains with respect to standard vaccine [29-31]. In the budget impact analysis an alternative scenario was developed to evaluate the economic performance of the vaccines in the hypothesis of a seasonal mismatch between the strains included in vaccines and the ones circulating. In this mismatch scenario the protection rate of the adjuvanted vaccine and standard was assumed to be limited at 85.5% and 56% respectively. These percentages were derived from the mean of the seroprotection rates measured in two different studies which analyzed four different heterovariant strains [29, 30].

A one-way sensitivity analysis was worked out to assess the robustness of the results provided by the budget impact model. In this analysis the model parameters were tested at the extremes of their CI95% when available. In the other case the parameters were tested in a ± 20% range, with some exceptions. The coverage rate was varied among the highest and lowest values recorded in Italian regions according the Italian Ministry of Health (Umbria: 77.5%; Friuli Venezia Giulia: 49.7%) [7]. The effectiveness of the adjuvanted vaccine in reducing ILI cases was varied by considering the protection rates demonstrated versus H3N2 and H1N1 viral strains, respectively greater and lower than the mean effectiveness in the base case analysis (B strain). The proportion of vaccines administered by the GP or in vaccine centers was tested with the extremes recorded in Italian regions, according to the national survey (administration by GP; Lazio 93.4%; 5.3% Sardegna) [20]. The incentive for the GP was tested between 0 and € 10. Finally the hospitalization costs were varied considering the highest and the lowest DRG tariffs in each category.

Results

The simulation with the budget impact model provided an estimate of the number of ILI cases, hospitalizations and deaths during an influenza season on the elderly Italian population (12 million subjects) (Tab. IV). The vaccination program with a coverage rate of 65.6% with the use of a traditional vaccine yielded a 26.9% reduction (about 552,000 cases) of ILI cases, while the MF59 adjuvanted vaccine yielded a 35.8% reduction (about 734,000 cases) with a relative increase of avoided cases of 33,1% (Fig. 1). On the mortality side the standard vaccine allowed reducing deaths by a 37.0% (10,700 deaths avoided) while the MF59 vaccine by a 45,6% (13,200 deaths avoided), with a relative increase of 23.1%. The number of hospitalizations for influenza and/or pneumonia was reduced by a 30.3% with the adjuvanted vac-

Tab. IV. ILI cases and related events in the base case and in the mismatch scenario, in the simulated population without vaccination, with the standard vaccination and with the MF59 vaccine.

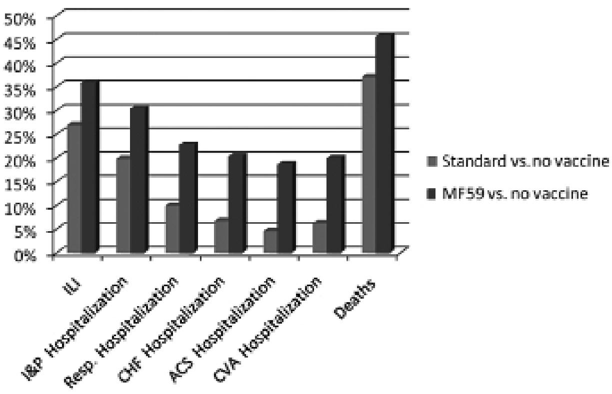
Events	No vaccine (n)	Standard vaccine (n)		MF59 vaccine (n)	
		Base case	Scenario	Base case	Scenario
ILI	2,050,687	1,499,134	1,741,817	1,316,690	1,423,120
I&P hospitalization	38,963	31,250	34,644	27,145	28,859
Resp. hospitalization	132,269	119,103	124,896	102,179	112,050
CHF hospitalization	28,299	26,394	27,233	22,551	24,787
ACS hospitalization	39,982	38,151	39,982	32,535	33,615
CVA hospitalization	62,776	58,862	62,776	50,285	52,096

ILI: influenza-like illness; ACS: acute coronary syndrome; CHF: congestive heart failure; CVA: cerebrovascular accident; I&P: influenza and pneumonia; RESP: respiratory complications.

cine (19.8% with the standard vaccine), while the ACS and CVA hospitalizations respectively by the 18.6% and 19.9% with the MF59 vaccine (4.6% and 6.2% with the standard vaccine). Finally the hospitalizations for respiratory complications and CHF were reduced respectively by a 22.7% and 20.3% with the adjuvanted vaccine (10.0% and 6.7% with the standard one).

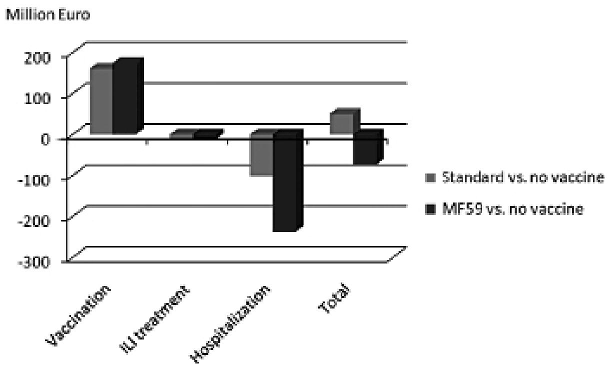
Total costs resulted lightly higher with the standard vaccine than without vaccination, with an overall +4.6% increase (about + € 50.2 million), while the use of the MF59 vaccine yielded a net saving of -6.8% (about € 74.0 million) with respect to non-vaccination (Tab. V). This means that, according to the results of this simulation, the initial cost for the vaccination program with

Fig. 1. Relative reductions of influenza related events obtained through the model simulation over the Italian elderly population along one influenza season with the standard and MF59 adjuvanted vaccines vs. the choice of no vaccine.



ILI: influenza-like illness; ACS: acute coronary syndrome; CHF: congestive heart failure; CVA: cerebrovascular accident; I&P: influenza and pneumonia; RESP: respiratory complications.

Fig. 2. Differences in total costs, acquisition and administration costs, visits and pharmaceutical treatment costs and hospitalization costs obtained through the model simulation over the Italian elderly population along one influenza season with the standard and MF59 adjuvanted vaccines vs. the choice of no vaccine.



ILI: influenza-like illness.

Tab. V. Total costs (Euro) in the base case and in the mismatch scenario for the simulated population due to ILI cases and related events, with use of the standard vaccine, the adjuvanted vaccine and for no vaccination.

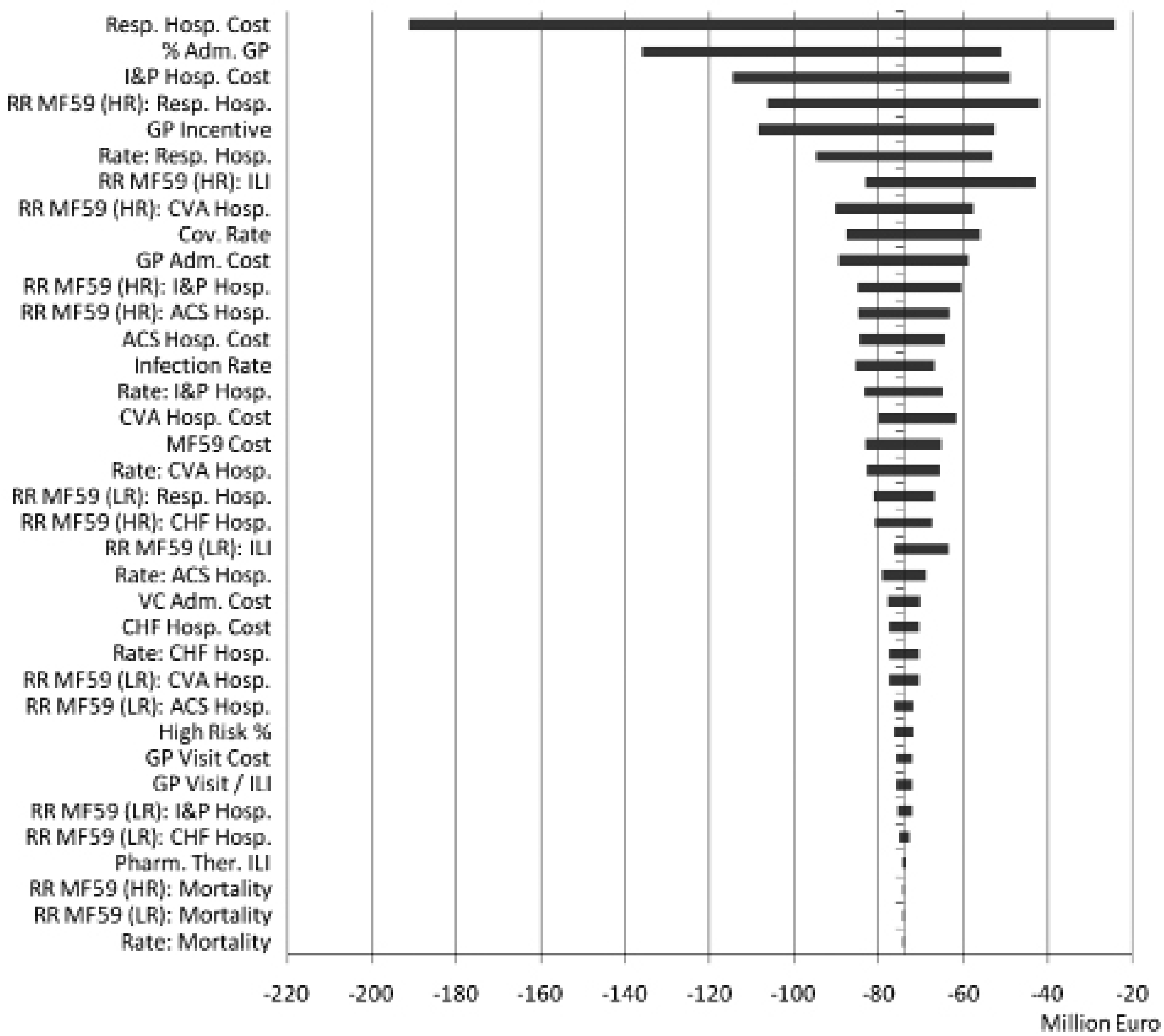
Items	No vaccine (Euro)	Standard vaccine (Euro)		MF59 vaccine (Euro)	
		Base case	Scenario	Base case	Scenario
Vaccine	-	160,501,294	160,501,294	174,674,471	174,674,471
GP visits	26,306,212	19,230,893	22,344,034	16,890,500	18,255,778
Antibiotics	6,582,705	4,812,221	5,591,234	4,226,575	4,568,214
I&P hospitalization	152,603,859	122,395,229	135,687,027	106,318,344	113,029,744
Resp. hospitalization	456,077,804	410,679,163	430,654,565	352,324,209	386,358,084
CHF hospitalization	87,488,126	81,598,537	84,189,956	69,715,870	76,628,401
ACS hospitalization	139,498,653	133,108,579	139,498,653	113,516,338	117,283,774
CVA hospitalization	216,819,969	203,302,166	216,819,969	173,675,686	179,931,607
Tot	1,085,377,329	1,135,628,083	1,195,286,732	1,011,341,993	1,070,730,072

ILI: influenza-like illness; ACS: acute coronary syndrome; CHF: congestive heart failure; CVA: cerebrovascular accident; I&P: influenza and pneumonia; RESP: respiratory complications; GP: General Practioners

the standard vaccine was nearly offset by healthcare resources savings obtained during the season. In the case of the MF59 vaccine the initial cost was totally offset, yielding to a final net saving (Fig. 2).
In the mismatch scenario, an influenza season with only heterovariant circulating virus strains was analyzed. In this alternative scenario, ILI cases and hospitalization events resulted more numerous than in base case for both the standard and adjuvanted vaccine due to their reduced protection against the heterovariant strain (Tab. V). Also on the cost side of the analysis the mismatch scenario got worse results as the total budget for one influenza season increased by +10.1% (about + € 109.9 million) with the standard vaccine vs. no vaccine. With the MF59 vaccine the final result is still a net saving of -1.3% (about € 14.6 million).

The one-way sensitivity analysis was performed on the total budget impact of the MF59 adjuvanted vaccination vs. no vaccination (base-case value was € -74 million). The results of this analysis, presented as tornado graphic, show an overall good stability of model's findings (Fig. 3). The parameter which can affect more the result is the unitary cost for hospitalization related to respiratory complications. In any case, under none of the variations considered, for model parameters the budget impact analysis of MF59 vs. no vaccination reversed its sign, meaning a relevant robustness of the final conclusion: the strategy has the capability of saving money. Interestingly enough in this analysis the purchasing cost of the MF59 vaccine is not among the most influential parameters in the model, as it is quite usual to see in budget impact models, supporting again the robustness of the conclusion.

Fig. 3. One-way sensitivity analysis on the total budget impact of the MF59 adjuvanted vaccination vs. no vaccination (base case value: € -74 million).



ILI: influenza-like illness; ACS: acute coronary syndrome; CHF: congestive heart failure; CVA: cerebrovascular accident; I&P: influenza and pneumonia; RESP: respiratory complications; Hosp: hospitalization; Adm: administration; RR: relative risk; HR: high risk group; LR: low risk group; Cov.: coverage; VC: vaccine center; Pharm. Ther.: pharmaceutical therapy; GP: General Practioners.

Discussion and conclusion

A large number of clinical and field studies highlights the importance of influenza vaccination programs among the elderly population. The results of the present budget impact analysis support this concept: the acquisition and administration costs to conduct a program with a standard vaccine are almost offset by the savings in other healthcare resources in one season. In the case of the MF59 adjuvanted vaccine those costs are more than repaid by the savings due to avoided hospitalizations. The same economic conclusion is reached under the mismatch scenario and the variations tested in the sensitivity analysis, demonstrating the good economic value of this type of vaccine.

In this budget impact analysis the cost perspective of the Italian SSN is adopted, so that only direct medical costs are considered. Nonetheless the vaccination program can induce a saving in costs that are directly borne by the patient or the family, like private visits or symptomatic treatments, not reimbursed by the Italian SSN. Indirect cost, such as reduced productivity, absenteeism or familiar care giving, can also play an important role in the definition of the total burden of influenza. The routine vaccination could also reduce the seasonal impact of these costs, which were not considered in the present analysis. It is very likely that if all the direct medical, patient-borne and indirect costs were considered and thus a broader social perspective adopted, also the vaccination program with the standard vaccine would result in a total net saving with respect the non-vaccination.

The major limitation of this analysis is related to the intrinsic and largely unavoidable limits of the modeling approach which invariably involves the use of multiple and non-homogeneous sources, extrapolation of data and, when no other information is available, the necessity for assumptions. These limits are common to all economic studies based on models. In general it is clear that the results of a model cannot be regarded by any mean as an absolute effectiveness claim, since the ultimate objective of a model-based economic analysis is always the comparative assessment of costs and outcomes of two or more healthcare technologies evaluated under the same set of assumptions (i.e. the model).

In conclusion, the use of MF59 adjuvanted vaccine in the place of the traditional vaccine for the routine seasonal influenza vaccination of the elderly population represents an effective option under both the clinical and the economic points of view.

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